EXHIBIT G

Civil Action No. 08-cv-2204 (JR)

EXHIBIT 3

Rec'd 3/17/04

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Baxter
BioScience

March 16, 2004

Felicia Eggleston, HCPCS Workgroup Coordinator
Centers for Medicare and Medicaid Services
Mailstop C5-08-27
7500 Security Boulevard
Baltimore, Maryland 21244-1850

RE: J-Code Request for Private Payer Use in Submitting Claims for ADVATE™ rAHF-PFM (Antihemophilic Clotting Factor [Recombinant], Plasma/Albumin-Free Method)

Dear Sir or Madam:

I am writing on behalf of Baxter BioScience (Baxter) to request that ADVATE™ rAHF-PFM (Antihemophilic Clotting Factor [Recombinant], Plasma/Albumin-Free Method) be considered eligible for assignment of a permanent, unique HCPCS J-code by the Centers for Medicare and Medicaid Services (CMS) HCPCS National Editorial Panel.[1] We are hopeful that the information provided during previous meetings between Baxter and CMS and the following submission will clarify the key differences between ADVATE™ rAHF-PFM and therapies reimbursed within the current HCPCS code (J7192) for recombinant factor VIII products. We believe these differences substantiate the need for a unique code for the plasma/albumin-free class of Factor VIII therapy.

ADVATE™ rAHF-PFM received FDA approval on July 25, 2003, for the prevention and control of bleeding episodes in patients with hemophilia A (classical hemophilia) and in the perioperative management of patients with hemophilia A. ADVATE™ rAHF-PFM became commercially available August 20, 2003.

ADVATE™ rAHF-PFM is the first factor VIII recombinant therapy to be prepared without the addition of any human- or animal-derived raw materials. The absence of human and animal materials eliminates concerns about infectious prions, which cause variant Creutzfeldt Jacob disease (vCJD), and other emerging pathogens. Fears about emerging and unknown pathogens have been an ongoing concern of the hemophilia community, which was devastated by both HIV/AIDS and Hepatitis C acquired from clotting factors administered in the 1960s, 1970s, and 1980s. The absence of human or animal derived materials in the processing or final formulation represents a significant advance in hemophilia treatment that differentiates ADVATE™ rAHF-PFM from therapies within the existing recombinant Factor VIII code.

[1] ADVATE is a trademark of Baxter International, Inc.

Below, we provide the Centers for Medicare and Medicaid Services (CMS) with the following:

- brief history of hemophilia treatment;
- brief overview of ADVATE™ rAHF-PFM,
- summary of the labeled indications for ADVATE™ rAHF-PFM, and
- reasons that ADVATE™ rAHF-PFM should be issued a permanent, unique HCPCS J-code for use in submitting claims for this plasma/albumin-free class of Factor VIII therapy.

We also supply the detailed information that CMS has requested for consideration for establishment of a HCPCS code. We have prepared this recommendation for your review in accordance with the HCPCS Code Modification Process for the 2005 HCPCS Update.

EVOLUTION OF HEMOPHILIA CARE AND IMPETUS FOR ADVATE'S DEVELOPMENT

In 1966 a process was developed and commercialized to separate and pool clotting factor from human plasma and distribute it on a widespread basis. For the first time, individuals with hemophilia were able to infuse this protein at home. This was a critical step forward in enabling persons with hemophilia to live nearly-normal lives.

Unfortunately, this therapeutic advance was accompanied by tragedy. Previously unknown pathogens entered undetected into the nation's blood supply and contaminated the plasma that was the source for these therapeutic proteins. As a consequence, thousands of individuals with hemophilia became infected with HIV and hepatitis C. Many individuals died or have been further disabled as a consequence.

Baxter and other processors of hemophilia clotting factors have instituted numerous safeguards to protect the safety of plasma derived therapeutic proteins. However, the fear of infection and the emergence of new and unknown pathogens—such as those that cause vCJD, the human equivalent of Mad Cow Disease—are an ongoing concern to the hemophilia community.

Among the advances in treatment is the availability of genetically engineered, also known as recombinant, clotting factors. Baxter introduced the first recombinant hemophilia clotting factor in 1992. First-generation recombinant Factor VIII proteins are processed by inserting the genetic code for Factor VIII into animal cells, which produce the human coagulation Factor VIII. The human Factor VIII is then purified and separated from animal cell components. While these therapies do not use human plasma as a source material, they utilize human and/or bovine components in the processing and/or final formulation of the therapy.

The National Hemophilia Foundation has continued to encourage processors of hemophilia clotting factors to develop therapies that do not utilize human or animal derivatives in any stage of formulation. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) made the following recommendation in November 2000.

> "Manufacturers of the recombinant products are strongly encouraged to avoid using human and animal proteins in manufacturing their products."[2]

The plasma/albumin-free method (PFM) of manufacturing ADVATE™ rAHF-PFM responds to this request.

BRIEF OVERVIEW OF ADVATE™ rAHF-PFM

Recombinant antihemophilic clotting factors (rAHFs) supply the Factor VIII protein that people with hemophilia A are missing, and need in order to prevent and control bleeding episodes. Currently, the recombinant Factor VIII protein is made by inserting the genetic code for Factor VIII into animal cells, which produce the human coagulation Factor VIII. The human Factor VIII is then purified and separated from animal cell components.

ADVATE™ rAHF-PFM represents a new category within rAHF products known as rAHF-PFM products, which are separate and distinct from the existing rAHF products described above. Baxter developed a new, proprietary process to make ADVATE™ rAHF-PFM. Like other rAHF products, ADVATE™ rAHF-PFM is not dependent on pools of human plasma as a source of Factor VIII protein.[3] However, unlike other rAHF products, the Chinese hamster ovary (CHO) cell line has been adapted to grow in a proprietary culture medium free of plasma, albumin, or any other human- or animal-derived additive.[4] ADVATE™ is therefore the first and only product produced without the addition of human or animal plasma proteins and albumin, thus eliminating the risk of viral and prion transmission that could be caused by pathogens found in these protein additives.

The unique derivation and purification processes involved in manufacturing ADVATE™ rAHF-PFM represent a new class of rAHF products. Because the currently available HCPCS J-code (J7192, *Factor VIII [antihemophilic factor, recombinant]*) does not describe the plasma/albumin-free method, Baxter is seeking unique billing codes to adequately describe ADVATE™ rAHF-PFM and ensure appropriate reimbursement.

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[2] MASAC Recommendation #106, "MASAC Recommendation Regarding the Use of Recombinant Clotting Factor Replacement Therapies," adopted by the National Hemophilia Foundation Board of Directors on November 12, 2000.

[3] Processed from a genetically engineered Chinese hamster ovary (CHO) cell line, ADVATE™ rAHF-PFM is a purified glycoprotein consisting of 2,332 amino acids. In culture, the CHO cell line expresses recombinant antihemophilic factor (rAHF) into the cell culture medium.

[4] The recombinant Factor VIII molecule is purified from the culture medium using immunoaffinity chromatography, followed by two ion exchange chromatography steps to bring it to an ultra high level of purity before finishing with a plasma/albumin-free final formulation. The hybridoma cell line for the murine antibody used in the immunoaffinity chromatography was adapted to grow in plasma/albumin-free cell culture conditions.

LABELED INDICATIONS FOR ADVATE™ rAHF-PFM

The FDA has approved ADVATE™ rAHF-PFM for the prevention and control of bleeding episodes in patients with hemophilia A (classical hemophilia) and in the perioperative management of patients with hemophilia A. ADVATE™ rAHF-PFM is not indicated for the treatment of von Willebrand's disease. A copy of the package insert is supplied in Appendix B.

REASONS FOR ISSUING A HCPCS J-CODE FOR ADVATE™ rAHF-PFM

Baxter requests that CMS eliminate a potential barrier to beneficiary access to ADVATE™ rAHF-PFM ADVATE—and future plasma/albumin-free clotting factors—by recognizing the unique characteristics of this therapy through the designation of a separate HCPCS J-code. Below, we outline compelling reasons why ADVATE™ rAHF-PFM would be an ideal candidate for creation of a product-specific J-code.

- **Absence of Human or Animal Materials Differentiates ADVATE™ rAHF-PFM**

  As described above, ADVATE™ rAHF-PFM is the first recombinant Factor VIII therapy to fulfill the National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council's (MASAC) request that human and animal derivatives be eliminated from the processing and final formulation of hemophilia clotting factors. Although the existing HCPCS code (J7192, *Factor VIII [antihemophilic factor, recombinant]*) describes the recombinant process, it does not reflect the difference between first-generation recombinant and plasma/albumin free technology. The formal request from NHF for a plasma/albumin free therapy shows the significance the hemophilia community places on this feature.

- **Providers Need Instruction on How to Bill For ADVATE™ rAHF-PFM**

  Providers of hemophilia therapies are acutely aware of continuing improvements in the derivation and manufacture of clotting factor products, and expect that second-generation therapies such as ADVATE™ rAHF-PFM will require new coding, billing, and claims processing procedures. Without a new Medicare billing code for a new class of therapies, physicians administering ADVATE™ rAHF-PFM and specialty pharmacies distributing products may be hesitant to submit initial ADVATE-related claims, significantly delaying the accumulation of up-to-date cost data by CMS.

- **Proper Classification Will Protect Patient Access**

  The classification of ADVATE™ rAHF-PFM and future plasma/albumin-free therapies within the existing recombinant factor VIII code may provide a disincentive for providers to supply this class of treatment to Medicare beneficiaries. Barriers to access are likely to occur because HCPCS codes that include multiple products work on the assumption that all therapies within a code have similar characteristics, even if second-generation therapies such as ADVATE™ rAHF-PFM represent greater technology- and safety-related costs. If there is a substantial difference between one or more therapies within a code, the reimbursement system may indirectly result in the provision of a less-advanced technology. The result is that patients will encounter significant barriers to access this new technology that has been specifically requested by the hemophilia community. In light of the recent

reductions in provider reimbursement, it will be increasingly critical that HCPCS codes include only products that are truly equivalent so treatment options will not be based upon reimbursement.

- **Elimination of Barriers to Access Will Encourage Investment**

  If patients are denied access to ADVATE™ rAHF-PFM as a result of provider reimbursement, companies in the process or considering the development of plasma/albumin free therapies may be reluctant to introduce new technology. This potential outcome would stunt innovation and undermine the hemophilia community's request for this class of therapy.

Below, Baxter provides information to support this request that ADVATE™ rAHF-PFM be considered among new pharmaceutical and biological products eligible for temporary S-codes issued quarterly by the Centers for Medicare and Medicaid Services (CMS) HCPCS National Editorial Panel.[5]

DETAILED INFORMATION REQUESTED BY CMS

1. **a) Trade Name of the Product:**

   ADVATE™ rAHF-PFM

   b) Generic Name of the Product:

   Antihemophilic Clotting Factor [Recombinant], Plasma/Albumin-Free Method

   c) FDA Classification of the Product:

   Biologic (Recombinant); documentation of initial FDA application is provided in Appendix A

[5] Baxter has submitted this request in accordance with the most up-to-date instructions posted by CMS on September 9, 2003, at http://cms.hhs.gov/medicare/hcpcs/.

2. Please circle the HCPCS category from the following list, which most accurately describes the category for the Item identified in question #1:

Medical/Surgical Supplies	Prosthetic	Drug
Dialysis Supplies and Equipment	Orthotic	(Biologic)
Ostomy/Urological Supplies	Enteral/Parenteral Nutrition	Radiopharmaceutical
Surgical Dressing	Durable Medical Equipment	Vision
	Blood/Blood Products	Hearing
		Other

3. Detailed Description of the Clinical Application of the Product:

a) Indications for Use:

The FDA has approved ADVATE™ rAHF-PFM for the prevention and control of bleeding episodes in patients with hemophilia A (classical hemophilia) and in the perioperative management of patients with hemophilia A. A copy of the package insert is supplied in Appendix B.

b) Method of Action:

ADVATE™ rAHF-PFM temporarily raises the level of Factor VIII in the blood to a level that allows blood clotting processes to function properly.

c) Dosage and Route of Administration:

With respect to dosing, the expected in vivo peak increase in Factor VIII level expressed as IU/dL of plasma or percent of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by 2. This calculation is based on the findings of several pharmacokinetic studies of rAHF concentrates,[6,7,8,9] and is supported by the data generated by 223 pharmacokinetic studies with ADVATE™ rAHF-PFM in 107 Phase 2/3 pivotal study subjects. These pharmacokinetic data demonstrated a peak post-infusion recovery of approximately 1.5-2.5 IU/dL per IU/kg above the pre-infusion baseline.

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[6] White II GC, Courter S, Bray GL, et al: A multicenter study of recombinant factor VIII (Recombinate™) in previously treated patients with hemophilia A. *Thromb Haemost* 77:660-667, 1997.
[7] Abshire TC, Brackmann H-H, Scharrer I, et al: Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy. *Thromb Haemost* 83:811-816, 2000.
[8] Lee CA, Owens D, Bray G, et al: Pharmacokinetics of recombinant factor VIII (Recombinate™) using one-stage clotting and chromogenic factor VIII assay. *Thromb Haemost* 82:1644-1647, 1999.
[9] Fijnvandraat K, Berntorp E, ten Cate JW, et al: Recombinant, B-domain deleted factor VIII (r-VIII SQ): Pharmacokinetics and initial safety aspects in hemophilia A patients. *Thromb Haemost* 77:298-302, 1997.

Examples (assuming patient's baseline Factor VIII level is < 1% of normal):

1. A dose of 1,750 IU ADVATE™ rAHF-PFM administered to a 70 kg patient should be expected to result in a peak post-infusion Factor VIII increase of 1750 IU x {[2IU/dL]/[IU/kg]}/[70 kg]= 50 IU/dL (50% of normal).
2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 70 IU/dL/{[2IU/dL]/[IU/kg]} x 40 kg = 1,400 IU.

A dose of ADVATE™ rAHF-PFM should be administered via bolus intravenous (IV) infusion over a period of ≤ 5 minutes (maximum infusion rate, [illegible] mL/min). The pulse rate should be determined before and during administration of ADVATE™ rAHF-PFM. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

Physician supervision of the treatment regimen is required. The careful control of substitution therapy is especially important in cases of major surgery or life-threatening hemorrhages. A detailed guide for dosing in the treatment of hemorrhages and in perioperative management is provided in the enclosed *Prescribing Information* (Appendix B).

d) Package Insert:

Please refer to Appendix B for full *Prescribing Information* for ADVATE™ rAHF-PFM. On the following page, we provide additional detail from the package insert not elsewhere provided in response to Item #3.

Manner of Packaging:

ADVATE™ rAHF-PFM is available in single-use vials, packaged with 5 mL sterile water for injection. The specific activity of ADVATE™ rAHF-PFM is 4000 to 10,000 IU per milligram of protein.[10] The package sizes available for ADVATE™ rAHF-PFM include the following amounts of antihemophilic factor (recombinant), plasma/albumin-free method:

NDC	Active Ingredient[11]
00944-2940-01	250 IU
00944-2940-02	500 IU
00944-2940-03	1,000 IU
00944-2940-04	1,500 IU

e) How Supplied:

ADVATE™ rAHF-PFM is available as a sterile, non-pyrogenic, white to off-white powder for intravenous injection.

[10] The potency assignment of IU per vial employs a Factor VIII concentrate standard that is referenced to a World Health Organization (WHO) International Standard for Factor VIII: C Concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.
[11] Package sizes are nominal.

4. FDA Marketing Approval Date:

ADVATE™ rAHF-PFM received marketing approval from the FDA on July 25, 2003, and the product became available shortly thereafter, on August 20, 2003. Documentation of the FDA marketing approval is supplied in Appendix C.

5. Date of Commercial Availability:

August 20, 2003

6. Primary and Customary Medical Purpose:

ADVATE™ rAHF-PFM is primarily and customarily used for medical purposes.

7. In Absence of Illness or Injury:

The use and/or efficacy of ADVATE™ rAHF-PFM in the absence of an illness or injury has not been evaluated. ADVATE™ rAHF-PFM is useful only in treatment of hereditary illness and control of bleeding episodes (treatment of injury) in patients with hemophilia A.

8. Prescription by Health Care Professional:

ADVATE™ rAHF-PFM is prescribed by physicians either in their offices or in hemophilia treatment centers (HTCs).

9. Beneficiary Access to Product:

Beneficiaries primarily obtain ADVATE™ rAHF-PFM through retail or specialty pharmacies for reconstitution and administration either in the patient's home or during routine visits to physician offices. Patients admitted to the hospital inpatient setting are prescribed ADVATE™ rAHF-PFM by physicians. Hospital outpatients may also obtain access to ADVATE™ rAHF-PFM via the hospital pharmacy.

10. Durability:

Individual packages of ADVATE™ rAHF-PFM are single-use products and are not designed for repeated use.

11. Current Options for Billing to Insurance Companies:

HCPCS codes are required in order to bill for hemophilia clotting factors in most settings of care. Providers submit either the UB-92 (hospital inpatient and outpatient claims) or CMS-1500 (physician office claims) forms in order to receive reimbursement from third-party payers.

In order to expedite third party payers' review of claims for ADVATE™ rAHF-PFM, providers may also choose to submit initial claims in hard copy (paper) format for manual review. These claims may include information supporting the use of not otherwise classified (NOC) HCPCS codes in place of J7192, including materials such as ADVATE™ rAHF-PFM's full *Prescribing Information*, which describe the unique derivation and purification processes used to manufacture ADVATE™ rAHF-PFM, and the product's enhanced safety profile due to the lack of plasma and albumin cultures. In addition, these claims may specify the National Drug Code (NDC) for the package of ADVATE™ rAHF-PFM administered.

12. Current Codes Used by Third-Party Payers to Process Claims:

Currently, there is no HCPCS code available for the new class of hemophilia therapy represented by ADVATE™ rAHF-PFM. Upon launching ADVATE™ rAHF-PFM, Baxter understood that CMS would be unable to consider a unique HCPCS billing code for ADVATE™ rAHF-PFM until April 1, 2004, and that, if granted, the code would not go into effect until January 1, 2005. In order to ease physician concerns about billing for a novel product that was not adequately described by existing HCPCS codes, Baxter instructed providers to use one of the not otherwise classified (NOC) codes listed below to bill for their initially prescribed doses of ADVATE™ rAHF-PFM.

HCPCS Code	Description
J3490	Unclassified drugs
J3590	Unclassified biologics
J7199	Hemophilia clotting factor, not otherwise classified

Of the above codes, J7199 *(Hemophilia clotting factor, not otherwise classified)* most accurately describes ADVATE™ rAHF-PFM; as a result, Baxter has notified private payers that providers may submit claims for ADVATE™ rAHF-PFM with J7199.

13. Inadequacy of Current Code Categories:

HCPCS codes are most widely used by the Medicare program, which separately reimburses for ADVATE™ rAHF-PFM in the hospital inpatient, hospital outpatient, physician office, and home care settings.[12] Many state Medicaid programs and private payers will also cover ADVATE™ rAHF-PFM in these settings.[13] However, private payers accept either HCPCS codes or National Drug Codes (NDCs)—depending on their preferences—for hemophilia clotting factors administered in the home care setting. For other settings of care where ADVATE™ rAHF-PFM is administered (including hospital inpatient, hospital outpatient, and physician office), private payers generally make payment under HCPCS codes only.

However, it would be inappropriate to advise providers to submit claims with the existing HCPCS code J7192, *Factor VIII (antihemophilic factor, recombinant)*, because this code does not accurately describe the plasma/albumin-free method unique to ADVATE™ rAHF-PFM. In addition, although Baxter has advised initial prescribers of ADVATE™ rAHF-PFM to submit claims using the NOC HCPCS codes described in #12 (above), some private payers

[12] Because self-administered hemophilia clotting factors are distributed via retail pharmacies and home infusion companies licensed as specialty pharmacies, claims must be filed with HCPCS codes.
[13] Unlike with Medicare claims, home infusion and specialty pharmacy providers will submit claims using primarily National Drug Codes (NDCs) under the Medicaid program.

and Medicare contracted carriers are reluctant to make payment under these codes. As a result, these prescribers of ADVATE™ rAHF-PFM are hesitant to submit claims until CMS creates an official HCPCS code specifically endorsed for use with private payers. In addition, current NOC HCPCS codes such as J7199 *(Hemophilia clotting factor, not otherwise classified)* can be used by hemophilia therapies besides ADVATE™ rAHF-PFM; as a result, use of J7199 may make it difficult for payers to track costs associated with ADVATE™ rAHF-PFM as distinct from other hemophilia therapies.

14. Market Distribution:

ADVATE™ rAHF-PFM is currently marketed nationwide. Recently, Baxter signed non-exclusive, multi-year agreements with multiple leading U.S. specialty pharmacy companies.[14]

15. Medicare Payment Status:

Hospital inpatient claims (UB-92): As a hemophilia clotting factor, ADVATE™ rAHF-PFM is paid separately in addition to the payment for the diagnosis related group (DRG). Payment is based on 95 percent of AWP. Providers must include the product-specific HCPCS code for the factor product administered, in addition to revenue code 0636 *(Drugs requiring detailed coding)*, in order to receive payment.

Hospital outpatient claims (UB-92): CMS includes hemophilia clotting factors, including ADVATE™ rAHF-PFM, in the category of blood products, which are currently paid separately (not "packaged" or "bundled") under their own ambulatory payment classifications (APCs) in addition to the APC payment for the administration procedure. HCPCS codes are required to bill for both the product and the infusion procedure.

Physician office claims (CMS-1500): ADVATE™ rAHF-PFM is scheduled to be included in the NOC drug pricing file in Q4 2004. Claims submitted with the NOC codes described above in #12 should be paid based on 95 percent of AWP.

Home infusion claims: Medicare covers self-administered hemophilia clotting factors. Patients obtain products through pharmacies, and pharmacies receive payment directly from Medicare.

16. Total Sales Volume To Date:

57 million units

[14] Source: "Baxter Announces U.S. Commercial Availability of ADVATE, Signs Multi-Year Supply Agreements with Major U.S. Specialty Pharmacy Customers," available as of September 12, 2003 at: http://advate.com/images/pdf/pr_advate_09_12_03_eng.pdf.

17. Utilization by Setting of Care:

Physician's Office:	5%
Freestanding Ambulatory Care Clinics:	
Patient's Home by Patient:	75%
Patient's Home by Health Care Provider:	10%
Nursing Home/Skilled Nursing Facility:	
Hospital Inpatient Facilities:	5%
Hospital Outpatient Facilities:	5%
Other (identify):	

18. Wholesale Cost of Item:

The current average wholesale prices (AWPs) for ADVATE™ rAHF-PFM—as determined and published by independent pricing services—are as follows:

NDC	00944-2940-01
Package Size:[15]	250 IU per single-dose vial + 5 mL sterile water for injection
AWP:	$1.66 per IU * 250 IU = $415.00
Date in Effect:	August 4, 2003
Source:	*Drug Topics® Red Book®*
AWP:	$1.88 per IU * 250 IU = $470.00
Date in Effect:	July 28, 2003
Source:	First Data Bank

NDC	00944-2940-02
Package Size:	500 IU per single-dose vial + 5 mL sterile water for injection
AWP:	$1.66 per IU * 500 IU = $830.00
Date in Effect:	August 4, 2003
Source:	*Drug Topics® Red Book®*
AWP:	$1.88 per IU * 500 IU = $940.00
Date in Effect:	July 28, 2003
Source:	First Data Bank

NDC	00944-2940-03
Package Size:	1,000 IU per single-dose vial + 5 mL sterile water for injection
AWP:	$1.66 per IU * 1,000 IU = $1,660.00
Date in Effect:	August 4, 2003
Source:	*Drug Topics® Red Book®*
AWP:	$1.88 per IU * 1,000 IU = $1,880.00
Date in Effect:	July 28, 2003
Source:	First Data Bank

[15] Package sizes are nominal.

NDC	00944-2940-04
Package Size:	1,500 IU per single-dose vial + 5 mL sterile water for injection
AWP:	$1.66 per IU * 1,500 IU = $2,490.00
Date in Effect:	August 4, 2003
Source:	*Drug Topics® Red Book®*
AWP:	$1.88 per IU * 1,500 IU = $2,820.00
Date in Effect:	July 28, 2003
Source:	First Data Bank

Third-party documentation of this AWP information is supplied in Appendix D.

19. Retail Cost of Item:[16]

The retail costs for ADVATE™ rAHF-PFM—as determined by Baxter—are as follows:

NDC	Retail Price
00944-2940-01	$1.08 per IU * 250 IU = $270.00
00944-2940-02	$1.08 per IU * 500 IU = $540.00
00944-2940-03	$1.08 per IU *1,000 IU = $1,080.00
00944-2940-04	$1.08 per IU *1,500 IU = $1,620.00

20. Manufacturers and Suppliers of Similar Items:

Several available antihemophilic clotting factor (recombinant) therapies share the same active ingredient as ADVATE™ rAHF-PFM, but do not share ADVATE™ rAHF-PFM's unique manufacturing and safety profile. These products are marketed under the same active ingredient category as ADVATE™ rAHF-PFM and include the following:

- Recombinate™, manufactured by Baxter Healthcare Corporation;
- Helixate® FS, manufactured by Bayer Pharmaceuticals, Inc. and distributed by Aventis Behring L.L.C.;
- Kogenate® FS, manufactured and distributed by Bayer Pharmaceuticals, Inc.; and
- ReFacto®, manufactured by Genetics Institute, Inc. and distributed by Wyeth.

[16] CMS defines current retail cost as the actual cost paid by hospitals net of all discounts, rebates, and incentives in cash or in kind.

21. Difference Between ADVATE™ rAHF-PFM and Competitor Products:

a) Item Cost:

Published AWPs for Select Hemophilia Therapies Compared to ADVATE™ rAHF-PFM

Product	*Drug Topics®* *Red Book®*	First Data Bank
Kogenate® FS	$1.68 per IU	$1.75 per IU
ADVATE™ rAHF-PFM	$1.66 per IU	$1.88 per IU
Helixate® FS	$1.44 per IU	$1.63 per IU
Recombinate™	$1.40 per IU	$1.63 per IU

b) Derivation and Purification:

While therapeutically similar to currently available recombinant antihemophilic clotting factor (rAHF) products, the unique biological nature of ADVATE™ rAHF-PFM sets it apart from comparable drugs within its class. Although rAHF concentrates are not dependent on pools of human plasma as a source of factor VIII protein, until the introduction of ADVATE™ rAHF-PFM, all rAHF agents still included the use of human- and animal-derived raw materials in the cell culture process, purification, and final formulation. The cell culture and purification steps used in the formulation of ADVATE™ rAHF-PFM employ no additives of human- or animal-derived raw materials. To further help ensure pathogen safety, the production process also includes a dedicated, viral inactivation solvent-detergent treatment step.

c) Clinical Studies:

A total of 114 previously treated study patients (PTPs) with severe or moderately severe hemophilia A (Factor VIII ≤ 2% of normal) were enrolled and treated in clinical studies of ADVATE™ rAHF-PFM. Of these, 108 were enrolled and treated in a Phase 2/3 multicenter pivotal study of pharmacokinetics, safety, hemostatic efficacy, and immunogenicity. Four of these subjects as well as 6 additional subjects were enrolled and treated in an open- label Phase 2/3 study of safety, efficacy, and immunogenicity of ADVATE™ rAHF-PFM in patients with hemophilia A who required surgical prophylaxis.

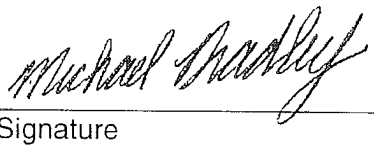
A global assessment of efficacy was rendered by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using an ordinal scale of excellent, good, fair, or none, based on the quality of hemostasis achieved with ADVATE™ rAHF-PFM for the treatment of each new bleeding episode. Of the 510 new bleeding episodes treated with ADVATE™ rAHF-PFM, 439 (86%) were rated excellent or good in their response to treatment, 61 (12%) were rated fair, 1 (0.2%) was rated as having no response, and for 9 (2%), the response to treatment was unknown. A total of 411 (81%) new bleeding episodes responded to a single infusion, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) required 4 or more infusions of ADVATE™ rAHF-PFM for satisfactory resolution. A total of 162 (32%) new bleeding episodes occurred spontaneously, 228 (45%) were the result of antecedent trauma, and for 120 (24%) bleeding episodes, the etiology was unknown.

The rate of new bleeding episodes during the protocol-mandated 75 exposure day prophylactic regimen (≥ 25 IU/kg body weight 3-4 times per week) was calculated as a function of the etiology of bleeding episodes for 107 evaluable subjects (n = 274 new bleeding episodes). The overall rate of bleeding as referenced by the degree of compliance was defined at a dose of > 25 IU/kg/infusion for > 80% of infusions and infusing > 3x/week for > 80% of weeks on the study.

HCPCS Coding Recommendation Submitted By Manufacturer:

Name:	Michael Bradley Senior Director, Healthcare Economics
Name of Corporation/ Organization:	Baxter BioScience Baxter Healthcare Corporation
Complete Mailing Address:	137 Glenview Drive Martinez, CA 94553
Telephone Number:	(925) 372-9096
FAX Number:	(925) 372-7579
E-mail Address:	Michael_b_bradley@baxter.com

I attest that the information provided in this HCPCS coding recommendation is accurate and correct to the best of my knowledge,



Signature — March 16, 2003 Date

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On behalf of Baxter, we thank you for your attention to this issue. Baxter would be happy to provide additional information about ADVATE™ rAHF-PFM that may assist you with this effort. Please feel free to contact me directly with any questions.

Attachments: Appendices (A-D)

Appendix A: Documentation of Initial FDA Application

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Baxter
BioScience

26 June 2002

Food and Drug Administration
Center for Biologics Evaluation and Research
Woodmont Office Center, Suite 200N
Document Control Room (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

BLA Original Application
ADVATE
Antihemophilic Factor (Recombinant),
Plasma/Albumin Free Method (rAHF-PFM)

Attention: Jay S. Epstein, M.D.
Director, Office of Blood Research and Review

Dear Dr Epstein:

Under 21 CFR section 601.2(a) and 601.20, Baxter Healthcare Corporation (Baxter) hereby submits an original biologic license application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM). The proposed tradename for rAHF-PFM is ADVATE.

This biologic license application is being submitted electronically in its entirety. The submission consists of two (2) 20/40 GB DLT tapes (one Archival copy, and one Review copy) in the format of NT Server 4.0 with backup exec 8.5 (Veritas). The size of the electronic submission is approximately 10 Gigabytes. The electronic data has been scanned for viruses with Symantec Norton AntiVirus 7.51.847 (Virus Definition File 40612g), and has been deemed virus free.

Per Agency request, four (4) copies of the clinical study reports are provided.

This submission contains trade secrets, thus the information is confidential and proprietary, and should not be disclosed to a third party without the express written consent of Baxter Healthcare Corporation.

If there are any regulatory or electronic questions regarding this submission, please contact Maria Munera at (818) 507-5571.

Sincerely,

Alan Morrison
Senior Director, Regulatory Affairs
Global Product Development

Enclosures: Two (2) DLT tapes (one Archival copy, one Review copy)
Four (4) copies of the clinical study reports

MM/sl
cc: A. Morrison/Vienna, A. Vidor/Glendale, M. Munera/Glendale

Appendix B: Package Insert/Full *Prescribing Information* for ADVATE™ rAHF-PFM

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM)

DESCRIPTION

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM) is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. In culture, the CHO cell line expresses recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF is purified from the culture medium using a series of chromatography columns. The cornerstone of the purification process is an immunoaffinity chromatography step in which a monoclonal antibody directed against Factor VIII is employed to selectively isolate the rAHF from the medium. The cell culture and purification processes used in the manufacture of ADVATE rAHF-PFM employ no additives of human or animal origin. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The rAHF synthesized by the CHO cells has the same biological effects as Antihemophilic Factor (Human) [AHF (Human)]. Structurally the recombinant protein has a similar combination of heterogeneous heavy and light chains as found in AHF (Human,

ADVATE rAHF-PFM is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. ADVATE rAHF-PFM is available in single-dose vials that contain nominally 250, 500, 1000 and 1500 International Units (IU) per vial. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximal amounts: 38 mg/mL mannitol, 10 mg/mL trehalose, 108 mEq/L sodium, 12 mM histidine, 12 mM Tris, 1.9 mM calcium, 0.17 mg/mL polysorbate-80, and 0.10 mg/mL glutathione. von Willebrand Factor (vWF) is co-expressed with FVIII, and helps to stabilize it in culture. The final product contains no more than 2 ng vWF/IU rAHF, which will not have any clinically relevant effect in patients with von Willebrand's Disease. The product contains no preservative.

Each vial of ADVATE rAHF-PFM is labeled with the AHF activity expressed in IU per vial. Biological potency is determined by an in vitro assay, which employs a Factor VIII concentrate standard that is referenced to a World Health Organization (WHO) International Standard for Factor VIII: C concentrates. The specific activity of ADVATE rAHF-PFM is 4000 to 10,000 IU per milligram of protein.

CLINICAL PHARMACOLOGY

The pharmacokinetics of ADVATE rAHF-PFM were investigated in a Phase 2/3 multicenter pivotal study of previously treated subjects. In addition, an interim analysis comparing the pharmacokinetics of ADVATE rAHF-PFM at the onset of treatment and after a period of at least 75 exposure days was performed in the context of an ongoing continuation study in subjects who completed treatment in the multicenter pivotal Phase 2/3 study. Post-infusion levels and clearance of Factor VIII during the perioperative period were examined in an interim analysis of subjects from the pivotal and continuation studies who were enrolled in an ongoing Phase 2/3 surgical study. Finally, the pharmacokinetics of ADVATE rAHF-PFM were investigated in an interim analysis of an ongoing study of pediatric previously treated subjects < 6 years of age (see Pediatric Use subsection under "PRECAUTIONS").

Pharmacokinetics

A randomized, crossover pharmacokinetic comparison of ADVATE rAHF-PFM produced at a pilot-scale facility in Orth, Austria (the test article) and RECOMBINATE rAHF (the control article) was conducted in the context of the pivotal Phase 2/3 study. Study subjects were initially infused with one of the two preparations at a dose of 50 ± 5 IU/kg body weight while in a non-bleeding state. The second study preparation was infused in a non-bleeding state at 50 ± 5 IU/kg after a washout period of 72 hours to 4 weeks following the first study infusion. The order in which each study preparation was administered was assigned by randomization. Pharmacokinetic parameters (area under the Factor VIII plasma concentration versus time curve [AUC], maximal post-infusion Factor VIII level [C_{max}], in vivo recovery, half-life, clearance [CL], mean residence time [MRT], and volume of distribution in steady-state [V_{ss}]) were calculated from Factor VIII activity measurements in blood samples obtained immediately before and at standardized time intervals up to 48 hours following each infusion.

A total of 56 study subjects were enrolled and randomized. Of these, 50 (modified intent-to-treat population) received both infusions of study medication and had sufficient pharmacokinetic data for the comparison of ADVATE rAHF and RECOMBINATE rAHF. Thirty subjects (per-protocol population) received both pharmacokinetic infusions of study medication and had data for all pharmacokinetic time points. Pharmacokinetic parameters for each study preparation in the per-protocol analysis are presented in Table 1.

Table 1.
Pharmacokinetic Parameters for ADVATE rAHF-PFM and RECOMBINATE rAHF (Per-Protocol Analysis)

Parameter	RECOMBINATE rAHF		ADVATE rAHF-PFM	
	N	Mean ± SD	N	Mean[a] ± SD
$AUC_{0\text{-}48h}$ (IU·h/dL)[a]	30	1530 ± 380	30	1534 ±436
In vivo recovery (IU/dL/IU/kg)[b]	30	2.59 ± 0.52	30	2.41 ± 0.50
Half-life (h)	30	11.24 ± 2.53	30	11.98 ± 4.28
C_{max} (IU/dL)	30	129 ± 27	30	120 ± 26
MRT (h)	30	20.03 ± 7.80	30	22.82 ± 13.94
V_{ss} (dL/kg)	30	0.58 ± 0.15	30	0.60 ± 0.15
CL (dL/kg/hr)	30	0.03 ± 0.01	30	0.03 ± 0.01

[a] Area under the plasma Factor VIII concentration x time curve from 0 to 48 hours post-infusion
[b] Calculated as (C_{max} - baseline Factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion Factor VIII measurement

For the pharmacokinetic parameters $AUC_{0\text{-}48h}$ and in vivo recovery, the 90% confidence intervals for the ratios of the mean values for the test and control articles were within the pre-established limits of 0.80 and 1.25 for both the per-protocol (n = 30) and intent-to-treat study (n = 50) populations. In addition, in vivo recovery at the onset of treatment and after 75 exposure days was compared for 62 subjects. Results of this analysis indicated no significant change in the vivo recovery at the onset of treatment and after ≥75 exposure days.

Additionally, the pharmacokinetics of ADVATE rAHF-PFM produced at the Orth facility were compared with those of ADVATE rAHF-PFM produced at a commercial-scale facility in Neuchatel, Switzerland. For the pharmacokinetic parameters $AUC_{0\text{-}48h}$ and in vivo recovery, the 90% confidence intervals for the ratios of the mean values for the test and control articles were within the pre-established limits of 0.80 and 1.25 for both the per-protocol and intent-to-treat study populations.

The Phase 2/3 continuation study provided a means for examining potential changes in all pharmacokinetic parameters of ADVATE rAHF-PFM at the onset of treatment and after a period of at least 75 exposure days. This comparison utilized data for ADVATE rAHF-PFM produced in the Orth facility obtained at the onset of treatment on the pivotal Phase 2/3 study with data for ADVATE rAHF-PFM produced in the Neuchatel facility obtained in the continuation study. A total of 13 of 34 eligible subjects were included in an interim per-protocol analysis (Table 2). Ninety-five percent (95%) confidence intervals calculated for the ratios of the mean values for $AUC_{0\text{-}48h}$ and in vivo recovery before and after at least 75 exposure days indicated no evidence of a difference in the pharmacokinetics of ADVATE rAHF-PFM at the two time points.

Table 2.
Pharmacokinetic Parameters for ADVATE rAHF-PFM Before and After at Least 75 Exposure Days

Parameter	Parameters at the Onset of Treatment[a]					Parameters after ≥ 75 Exposure Days[b]				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
$AUC_{0\text{-}48h}$ (IU·h/dL)	13	1315	405	876	2314	13	1262	497	831	2731
C_{max} (IU/dL)	13	111	23	77	151	13	111	25	73	151
Adjusted Recovery (IU/dL/IU/kg)	13	2.24	0.47	1.54	3.02	13	2.20	0.51	1.46	3.06
Total AUMC (IU·h²/dL)	13	32995	31768	10527	129569	13	28231	23573	10065	100710
Half-life (h)	13	11.10	2.72	8.38	17.96	13	10.89	1.37	9.24	13.92
Clearance (dL/(kg·h)	13	0.04	0.01	0.02	0.06	13	0.04	0.01	0.01	0.06
Mean residence time (h)	13	19.15	8.40	9.80	40.56	13	18.14	5.32	9.39	29.82
V_{ss} (dL/kg)	13	0.64	0.13	0.42	0.90	13	0.68	0.16	0.43	0.94

[a] Data from the Phase 2/3 pivotal study for ADVATE rAHF-PFM produced in Orth
[b] Data from the Phase 2/3 continuation study for ADVATE rAHF-PFM produced in Neuchâtel

In an interim analysis of data from 10 of 25 planned subjects in the Phase 2/3 surgery study, the target Factor VIII level was met or exceeded in all cases following a single loading dose ranging from 48.0 to 69.8 IU/kg.

Hemostatic Efficacy

In the Phase 2/3 pivotal study, a global assessment of efficacy was rendered by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using an ordinal scale of excellent, good, fair, or none, based on the quality of hemostasis achieved with ADVATE rAHF-PFM produced in the Orth facility for the treatment of each new bleeding episode. A total of 510 bleeding episodes were reported, with a mean (± SD) of 6.1 ± 8.2 bleeding episodes per subject. Of the 510 new bleeding episodes treated with ADVATE rAHF-PFM, 439 (86%) were rated excellent or good in their response to treatment, 61 (12%) were rated fair, 1 (0.2%) was rated as having no response, and for 9 (2%), the response to treatment was unknown. A total of 411 (81%) new bleeding episodes were managed with a single infusion, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) required 4 or more infusions of ADVATE rAHF-PFM for satisfactory resolution. A total of 162 (32%) new bleeding episodes occurred spontaneously, 228 (45%) were the result of antecedent trauma, and for 120 (24%) bleeding episodes, the etiology was unknown.

The rate of new bleeding episodes during the protocol-mandated 75 exposure day prophylactic regimen (≥ 25 IU/kg body weight 3-4 times per week) was calculated as a function of the etiology of bleeding episodes for 107 evaluable subjects (n = 274 new bleeding episodes). These rates are presented in Table 3.

Table 3.
Rate of New Bleeding Episodes During Prophylaxis

Bleeding Episode Etiology	Mean (± SD) New Bleeding Episodes/Subject/Month
Spontaneous	0.34 ± 0.49
Post-traumatic	0.39 ± 0.46
Unknown[a]	0.33 ± 0.34
Overall	0.52 ± 0.71

[a] Etiology was indeterminate

In a post-hoc analysis, the overall rate of bleeding was correlated inversely with the degree of compliance with the prescribed prophylactic regimen. Subjects who infused less than 25 IU ADVATE rAHF-PFM per kg per dose for more than 20% of prophylactic infusions or administered less than 3 infusions per week for more than 20% of study weeks (n = 37) experienced a 2.3-fold higher rate of bleeding in comparison with subjects who complied with the prescribed prophylactic regimen at least 80% of the time and for ≥ 80% of doses (n = 70).

The Phase 2/3 continuation study involved subjects previously treated on the pivotal Phase 2/3 study and provided additional efficacy data on ADVATE rAHF-PFM. An interim analysis of efficacy was conducted for 27 of 82 enrolled subjects who self-administered ADVATE rAHF-PFM produced in Neuchâtel on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE rAHF-PFM. As in the pivotal Phase 2/3 study, new bleeding episodes were treated with ADVATE rAHF-PFM and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved.

A total of 51 new bleeding episodes occurred in 13 of the 27 subjects being treated with ADVATE rAHF-PFM. By etiology, 53% of these bleeding events resulted from trauma and 27% occurred spontaneously; the other 20% had an undetermined etiology. The response to treatment with ADVATE rAHF-PFM for the majority (63%) of all new bleeding episodes was rated as excellent or good. In addition, 86% of the bleeding episodes resolved with only 1 infusion and an additional 6% were resolved by a second infusion. Thus, 92% of all bleeding episodes required 1 or 2 infusions of study product.

An interim analysis of the hemostatic efficacy of ADVATE rAHF-PFM during the perioperative management of subjects undergoing surgical procedures was conducted for 10 of 25 planned subjects. Ten subjects underwent 10 surgical procedures while receiving ADVATE rAHF-PFM. Eight subjects received the test product by intermittent bolus infusion and 2 subjects received a combination of continuous and intermittent bolus infusion. Nine of the 10 subjects completed the study. Six of the surgical procedures were classified as major, and 4 were minor. Of the 6 major surgeries, 5 were for orthopedic complications of hemophilia. A brief description of each surgical procedure, along with study duration and study medication exposure, are presented in Table 4.

Table 4.
Surgical Procedures, Study Duration, and Study Medication Exposure

Surgery Type	Days of Study	ADVATE rAHF-PFM Exposure Days	Cumulative ADVATE rAHF-PFM Exposure (IU)
Total hip replacement	16	15	61,600
Knee joint replacement	22	18	76,060
Knee arthrodesis	24	22	66,080
Transposition of the left ulnar nerve	5	3	14,560
Insertion of Mediport	28	8[a]	46,893
Dental extraction	18	6	16,599
Left elbow synovectomy	43	32	102,180
Teeth extraction	2	2	10,350
Right knee arthroscopy, chondroplasty and synovectomy	13	10[a]	32,334
Wisdom teeth extraction	14	5	15,357

[a] ADVATE rAHF-PFM was administered by continuous infusion for the first 48 hours post-operatively, followed by bolus infusions for the remainder of study treatment.

For each of the 10 subjects, intra- and post-operative quality of hemostasis achieved with ADVATE rAHF-PFM was assessed by the operating surgeon and study site investigator, respectively, using an ordinal scale of excellent, good, fair, or none. The same rating scale was used to evaluate control of hemorrhage from a surgical drain placed at the incision site in one subject. The quality of hemostasis achieved with ADVATE rAHF-PFM was rated as excellent or good for all assessments.

INDICATIONS AND USAGE

ADVATE rAHF-PFM is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. ADVATE rAHF-PFM is also indicated in the perioperative management of patients with hemophilia A. ADVATE rAHF-PFM can be of therapeutic value in patients with Factor VIII inhibitors not exceeding 10 Bethesda Units (BU) per mL.[1, 2] However, in patients with a known or suspected

inhibitor to Factor VIII, the plasma Factor VIII level should be monitored frequently and the dose of ADVATE rAHF-PFM should be adjusted accordingly.

ADVATE rAHF-PFM is not indicated for the treatment of von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse or hamster proteins may be a contraindication to the use of ADVATE rAHF-PFM (see **PRECAUTIONS**). Known intolerance or allergic reaction to any of the constituents in the formulation may be a contraindication to the use of ADVATE rAHF-PFM. ADVATE rAHF-PFM is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.

WARNINGS

None.

PRECAUTIONS

General

Identification of the clotting defect as Factor VIII deficiency is essential before the administration of ADVATE rAHF-PFM. No benefit may be expected from this product in treating other coagulation factor deficiencies.

Formation of Inhibitors to Factor VIII

The formation of neutralizing antibodies to Factor VIII (Factor VIII inhibitors) is a known complication in the management of individuals with hemophilia A. The reported prevalence of these antibodies in previously-untreated patients who were administered rAHF products over several years is 20.7 to 31.7%.[3, 4, 5, 6, 7, 8] These inhibitors are invariably of the immunoglobulin G (IgG) isotype, and the Factor VIII inhibitory activity is expressed as BU per mL of plasma. Patients treated with AHF products should be carefully monitored for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests.

Factor VIII inhibitor testing was performed throughout all studies in the rAHF-PFM clinical program. Among 136 treated subjects ≥10 years of age, all of whom had ≥ 150 exposure days to Factor VIII products at study entry, 102 had at least 75 exposure days to ADVATE rAHF-PFM. None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE rAHF-PFM while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE rAHF-PFM exposure days. Eight weeks later, the inhibitor was no longer detectable, and in vivo recovery was normal at 1 and 3 hours after infusion of RECOMBINATE rAHF. For the group comprising all subjects with at least 75 exposure days to ADVATE rAHF-PFM and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02 to 5.4 %.

An interim analysis of inhibitor development in 15 of 50 planned pediatric subjects < 6 years of age who had at least 50 prior exposure days to factor VIII at study entry was conducted. No subject completed 50 exposure days to ADVATE rAHF-PFM. Ten of the 15 enrolled subjects completed at least 10 exposure days to ADVATE rAHF-PFM or 120 total days on study; among this subset, there were no inhibitors.

Formation of Antibodies to Mouse or Hamster Protein

ADVATE rAHF-PFM contains trace amounts of mouse immunoglobulin G (MuIgG; maximum of 0.1 ng/IU ADVATE rAHF-PFM) and hamster (CHO) proteins (maximum of 1.5 ng/IU ADVATE rAHF-PFM). As such, there exists a remote possibility that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

In the Phase 2/3 pivotal study of ADVATE rAHF-PFM, serum samples were tested by enzyme immunoassays at baseline and after every 15 ± 2 exposure days, for the presence of antibodies to CHO protein and MuIgG. Regression analysis of assay results was conducted to evaluate trends in levels of antibodies to heterologous proteins as a function of time on study. Four study subjects showed a statistically significant increasing trend in the levels of anti-CHO (n = 1) or anti-MuIgG (n = 3) antibody levels over the course of the study. A fifth study subject showed a marked increase in anti-MuIgG antibodies coincident with the 60 and 75 exposure day interval study visits. None of these subjects exhibited adverse experiences (AEs) or other study findings consistent with an allergic or hypersensitivity response.

Information For Patients

Although allergic type hypersensitivity reactions were not observed in any study subjects receiving ADVATE rAHF-PFM, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician immediately if these symptoms occur.

Laboratory Tests

Although the dose can be estimated by the calculations that follow, it is highly recommended that, whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

If the patient's plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after adequate dosing, the presence of an inhibitor should be suspected. By performing the appropriate laboratory procedures, the presence of an inhibitor can be demonstrated and quantified in terms of the number of BU per mL (i.e. the amount of Factor VIII activity neutralized by one mL of patient plasma). If the inhibitor is present at levels less than 10 BU per mL, the administration of additional AHF concentrate may neutralize the

inhibitor, and may permit an appropriate hemostatic response. The close monitoring of plasma Factor VIII levels by laboratory assays is necessary in this situation.

Inhibitor titers above 10 BU per mL are likely to make the control of hemostasis with AHF concentrates either impossible or impractical because of the very large dose required. In addition, the inhibitor titer may rise following AHF infusion as a result of an anamnestic response to Factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies were conducted with the active ingredient in ADVATE rAHF-PFM to assess its mutagenic or carcinogenic potential. The CHO cell line employed in the production of ADVATE rAHF-PFM is derived from that used in the biosynthesis of RECOMBINATE rAHF. ADVATE rAHF-PFM has been shown to be comparable to RECOMBINATE rAHF with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology and toxicology.[9] By inference, RECOMBINATE rAHF and ADVATE rAHF-PFM would be expected to have equivalent mutagenic and carcinogenic potential.

RECOMBINATE rAHF was tested for mutagenicity at doses considerably exceeding plasma concentrations in vitro, and at doses up to ten times the expected maximal clinical dose in vivo. At that concentration, it did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei formation in bone marrow polychromatic erythrocytes. Studies in animals have not been performed to evaluate carcinogenic potential.

Pediatric Use

Use of ADVATE rAHF-PFM is being examined in the context of an ongoing study of previously treated subjects under 6 years of age and in a planned study of previously untreated subjects with severe or moderately severe hemophilia A. In addition, pediatric subjects between 10 and 16 years of age were treated on the Phase 2/3 pivotal study, and those over 5 years of age were eligible for treatment on the ongoing Phase 2/3 surgery study.

A total of 54 subjects ≤16 years of age have been treated across all studies of ADVATE rAHF-PFM to date. Interim pharmacokinetic data for 34 subjects (per-protcol analysis population) ≤ 16 years of age were obtained from a combined dataset comprising subjects 10 to 16 years of age treated on the Phase 2/3 pivotal study and subjects enrolled and treated on the ongoing study of pediatric previously treated subjects < 6 years of age. Among these, 0 were neonates (birth to < 1 month of age), 2 were infants (1 month to < 2 years of age), 15 were children (2 to 12 years of age), and 17 were adolescents (12 to ≤ 16 years of age).

Pharmacokinetic parameters were not significantly different for the different age categories. A summary of the pharmacokinetic parameters for the 34 subjects ≤ 16 years of age in the per-protocol analysis population are shown in Table 5. The mean (± SD) plasma half-life was 11.21 ± 2.92 hours (range: 8.31- 24.7 hours). The mean $AUC_{0\text{-}48h}$ was 1363 ± 440 IU·h/dL. The mean values for C_{max} and adjusted recovery were 109 ± 23 IU/dL and 2.17 ± 0.44 IU/dL / IU/kg, respectively.

Table 5.
Pharmacokinetic Parameters with ADVATE rAHF-PFM in Pediatric Previously Treated Subjects (Per-protocol Analysis)

	N	Mean	SD	Min	Max
$AUC_{0\text{-}48h}$ (IU·h/dL)	34	1363	440	792	2398
C_{max} (IU/dL)	34	109	23	62	181
Adjusted Recovery (IU/dL/IU/kg)	34	2.17	0.44	1.23	3.39
Total AUMC (IU·h²/dL)	34	36823	47250	9749	283097
Half-life (h)	34	11.21	2.92	8.31	24.7
Clearance (dL/(kg·h))	34	0.04	0.01	0.01	0.06
Mean residence time (h)	34	19.79	9.92	10.70	66.66
V_{ss}(dL/kg)	34	0.64	0.12	0.32	0.86

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ADVATE rAHF-PFM. It is not known whether ADVATE rAHF-PFM can cause fetal harm when administered to a pregnant woman, or whether it can affect reproductive capacity. ADVATE rAHF-PFM should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Adverse reactions were examined among a total of 96 subjects > 16 years of age and 54 subjects ≤ 16 years of age who received at least one infusion of ADVATE rAHF-PFM. For subjects > 16 years of age, the mean ± SD and median (range) values for time on study per subject were 319 ± 213 days and 403 days (1 to 654); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 130 ± 84 days and 140 days (1 to 289); and the mean ± SD and median (interquartile range) IU/kg per infusion were 32.0 ± 8.27 IU/kg and 30.7 IU/kg (27.8 to 33.8).

For subjects ≤ 16 years of age, the mean ± SD and median (range) values for time on study per subject were 321 ± 210 days and 428 days (1 to 651); the mean ± SD and median (range) exposure days to ADVATE rAHF-PFM per subject were 138 ± 93 days and 181 days (1 to 284); and the mean ± SD and median (interquartile range) IU/kg per infusion were 36.5 ± 11.7 IU/kg and 33.4 IU/kg (29.7 to 40.4).

Across all clinical studies, a total of 1304 adverse events were reported among 128 of the 150 subjects who received at least 1 infusion of ADVATE rAHF-PFM. Of the 1304 adverse events, 696 were reported among 85 subjects > 16 years of age and 608 were reported among 43 subjects ≤ 16 years of age. All adverse events (product-related and unrelated) reported by at least 10% of subjects are shown in Table 6.

Table 6.
Summary of All Adverse Experiences (Product-Related and Unrelated) that Occurred in Greater than or Equal to 10% of Study Subjects

MedDRA System Organ Class	MedDRA Preferred Term	Number of Events	Number of Subjects	Percent of Evaluable Subjects[a]
Gastrointestinal disorders	Pharyngolaryngeal pain	22	17	11.3
General disorders and administration site conditions	Fall	25	19	12.7
	Pyrexia	37	25	16.7
Infections and infestations	Nasopharyngitis	32	22	14.7
Injury, poisoning and procedural complications	Accident nos	62	26	17.3
	Limb injury nos	195	52	34.7
Musculoskeletal and connective tissue disorders	Arthralgia	74	35	23.3
Nervous system disorders	Headache nos	138	44	29.3
Respiratory, thoracic and mediastinal disorders	Cough	37	23	15.3

[a] Percent relative to 150, the total number of subjects across all studies who received at least one infusion of ADVATE rAHF-PFM

Eighteen of the 1304 adverse events were deemed serious; none were related to the study medication. There were no deaths. Among the 1286 non-serious adverse events, only 28 in 12 subjects were judged by the investigator to be related to the study drug. Severity ratings among the 28 events were mild in 8 cases, moderate in 16 cases, and severe in 4 cases (Table 7).

Table 7.
Summary of Non-Serious, Study-Drug Related Adverse Events

Severity	MedDRA Preferred Term	Number of Events
Mild	Dysgeusia	3
	Pruritis	1
	Dizziness	1
	Catheter-related infection	1
	Rigors	1
	Headache nos	1
	Total	8
Moderate	Dysgeusia	1
	Dizziness	2
	Headache nos	1
	Hot flushes	2
	Diarrhoea nos	1
	Oedema lower limb	1
	Sweating increased	1
	Nausea	1
	Dyspnoea nos	1
	Abdominal pain upper	1
	Chest pain	1
	Bleeding tendency[a]	1
	Haematocrit decreased	1
	Joint Swelling	1
	Total	16
Severe	Headache nos	1
	Pyrexia	1
	Haematoma nos	1
	Coagulation factor VIII decreased	1
	Total	4

[a] Recorded as prolonged bleeding after postoperative drain removal on the case report form

The unexpected decreased coagulation factor VIII levels occurred in one subject during continuous infusion of ADVATE rAHF-PFM following surgery (postoperative Days 10-14). Hemostasis was maintained at all times during this period and both plasma Factor VIII levels and clearance rates returned to appropriate levels by postoperative Day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.

Factor VIII inhibitor testing was performed throughout all studies in the rAHF-PFM clinical program. Among 136 treated subjects ≥10 years of age, all of whom had ≥ 150 exposure days to Factor VIII products at study entry, 102 had at least 75 exposure days to ADVATE rAHF-PFM. None of these subjects developed an inhibitor.

One subject who had < 50 exposure days to ADVATE rAHF-PFM while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE rAHF-PFM exposure days. Eight weeks later, the inhibitor was no longer detectable, and in vivo recovery was normal at 1 and 3 hours after infusion of RECOMBINATE rAHF. For the group comprising all subjects with at least 75 exposure days to ADVATE rAHF-PFM and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02 to 5.4.

DOSAGE AND ADMINISTRATION

Each vial of ADVATE rAHF-PFM is labeled with the rAHF activity expressed in IU per vial. This potency assignment employs a Factor VIII concentrate standard that is referenced to a WHO International Standard for Factor VIII:C Concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

The expected in vivo peak increase in Factor VIII level expressed as IU/dL of plasma or percent of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by 2. This calculation is based on the findings of several pharmacokinetic studies of rAHF concentrates,[10, 11, 12, 13] and is supported by the data generated by 223 pharmacokinetic studies with ADVATE rAHF-PFM in 107 Phase 2/3 pivotal study subjects. These pharmacokinetic data demonstrated a peak post-infusion recovery of approximately 1.5-2.5 IU/dL per IU/kg above the pre-infusion baseline.

Examples (assuming patient's baseline Factor VIII level is < 1% of normal):

1. A dose of 1,750 IU ADVATE rAHF-PFM administered to a 70 kg patient should be expected to result in a peak post-infusion Factor VIII increase of 1750 IU x {[2IU/dL]/[IU/kg]}/[70 kg]= 50 IU/dL (50% of normal).
2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 70 IU/dL/{[2IU/dL]/[IU/kg]} x 40 kg = 1400 IU.

Recommended Dose Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of hemorrhages is provided in Table 8. A guide for dosing in perioperative management is provided in Table 9. The careful control of replacement therapy is especially important in cases of major surgery or life-threatening hemorrhages.

Table 8.
Guide to ADVATE rAHF-PFM Dosing for Treatment of Hemorrhages

Degree of Hemorrhage	Required Peak Post infusion Factor VIII Activity in the Blood (as % of normal or IU/dL)	Frequency of Infusion
Early hemarthrosis, muscle bleeding episode, or mild oral bleeding episode	20-40	Begin infusions every 12 to 24 hours for one to three days until the bleeding pisode is resolved (as indicated by relief of pain) or healing is achieved.
More extensive hemarthrosis, muscle bleeding episode, or hematoma	30-60	Repeat infusions every 12 to 24 hours for (usually) three days or more until pain and disability are resolved.
Life-threatening bleeding episodes such as head injury, throat bleeding episode, or severe abdominal pain	60-100	Repeat infusions every 8 to 24 hours until resolution of the bleeding episode has occurred.

Table 9:
Guide to ADVATE rAHF-PFM Dosing for Surgical Procedures

Type of Procedure	Required Peak Post infusion Factor VIII Activity in the Blood (as % of Normal or IU/dL)	Frequency of Infusion
Minor surgery, including tooth extraction	60-100	Give a single bolus infusion beginning within one hour of the operation, with optional additional dosing every 12 – 24 hours as needed to control bleeding. For dental procedures, adjunctive adjunctive therapy may be considered.
Major surgery	80-120 (pre- and post-operative)	For bolus infusion replacement, repeat infusions every 8 to 24 hours, depending on the desired level of Factor VIII and state of wound healing.

Although dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial Factor VIII activity assays be perf ɪrmed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

Reconstitution: Use Aseptic Technique

1. Bring the ADVATE rAHF-PFM (dry concentrate) and Sterile Water for Injection (diluent) to room temperature.
2. Remove caps from the concentrate and diluent vials.
3. Cleanse stoppers with germicidal solution, and allow to dry prior to use.
4. Remove protective covering from one end of the double-ended needle and insert exposed needle through the center of the stopper.
5. Remove protective covering from the other end of the double-ended needle. Invert diluent bottle over the upright ADVATE rAHF-PFM bottle, then rapidly insert the free end of the needle through the ADVATE rAHF-PFM bottle stopper at its center. The vacuum in the bottle will draw in the diluent.
6. Disconnect the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the ADVATE rAHF-PFM bottle. Swirl gently until all material is dissolved. Be sure that ADVATE rAHF-PFM is completely dissolved, otherwise active materials will be removed by the filter needle.

NOTE: Do not refrigerate after reconstitution.

Administration: Use Aseptic Technique

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. A colorless appearance is acceptable for ADVATE rAHF-PFM. ADVATE rAHF-PFM should be administered at room temperature not more than 3 hours after reconstitution. Plastic syringes must be used with this product, since proteins such as ADVATE rAHF-PFM tend to stick to the surface of glass syringes.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
2. Insert needle into reconstituted ADVATE rAHF-PFM.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under **Administration by bolus infusion.**
5. If a patient is to receive more than one bottle of ADVATE rAHF-PFM, the contents of the multiple bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. Filter needles are intended to filter the contents of a single bottle of ADVATE rAHF-PFM only.

Administration by bolus infusion

A dose of ADVATE rAHF-PFM should be administered over a period of ≤ 5 minutes (maximum infusion rate, 10 mL/min). The pulse rate should be determined before and during administration of ADVATE rAHF-PFM. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

HOW SUPPLIED

ADVATE rAHF-PFM is available in single-dose vials that contain nominally 250, 500, 1000, and 1500 IU per vial. ADVATE rAHF-PFM is packaged with 5 mL of Sterile Water for Injection, a double-ended needle, a filter needle, infusion set/blood collection set*, 10 mL sterile syringe, alcohol swabs, bandages, one full prescribing physician insert, and one patient insert.

STORAGE

ADVATE rAHF-PFM should be refrigerated (2° - 8°C [36° - 46°F]). Avoid freezing to prevent damage to the diluent vial. ADVATE rAHF-PFM may be stored at room temperature (22° - 28°C [72° - 82°F]) for a period of up to 6 months until the expiration date. Do not use beyond the expiration date printed on the vial.

* Approved for both indications under 510(k).

REFERENCES

1. Aledort L: Inhibitors in hemophilia patients: Current status and management. Am J Hematol 47:208-217, 1994.
2. Kessler CM: An introduction to factor VIII inhibitors: The detection and quantitation. Am J Med 91 (Suppl 5A):1S-5S, 1991.
3. Lusher J, Arkin S, Hurst D: Recombinant FVIII (Kogenate) treatment of previously untreated patients (PUPs) with hemophilia A. Update of safety, efficacy and inhibitor development after seven study years. Abstract no. PD?664, ISTH, Florence. Thromb Haemost (suppl.):162, 1997.
4. Gruppo R, Chen H, Schroth P, Bray GL: Safety and immunogenicity of recombinant factor VIII (Recombinate) in previously untreated patients (PUPs): A 7.3 year update. Abstract no. 291, XXIII Congress of the World Federation of Haemophilia, The Hague. Haemophilia 4:228, 1998.
5. Rothschild C, Laurian Y, Satre EP, et al: French previously untreated patients with severe hemophilia A after exposure to recombinant factor VIII: Incidence of inhibitor and evaluation of immune tolerance. Thromb Haemost 80:779-783, 1998.
6. Gringeri A, Kreuz W, Escuriola-Ettinghausen C, et al: Anti-FVIII inhibitor incidence in previously untreated patients (PUPs) with hemophilia exposed to Kogenate (G.I.P.S.I.-German-Italian PUP Study on Inhibitor). Abstract no. 2642, ISTH, Florence. Thromb Haemost (suppl.):648, 1997.
7. Courter SG, Bedrosian CL: Clinical evaluation of B-domain deleted recombinant factor VIII in previously untreated patients. Semin Hematol 38:52-59, 2001.
8. Scharrer I, Bray GL, Neutzling O: Incidence of inhibitors in haemophilia A patients - A review of studies of recombinant and plasma-derived factor VIII concentrates. Haemophilia 5:45-54, 1999.
9. Baxter Healthcare Corporation, Glendale, CA. U.SA. Data on file, 2002.
10. White II GC, Courter S, Bray GL, et al: A multicenter study of recombinant factor VIII (Recombinate™) in previously treated patients with hemophilia A. Thromb Haemost 77:660-667, 1997.
11. Abshire TC, Brackmann H-H, Scharrer I, et al: Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy. Thromb Haemost 83:811-816, 2000.
12. Lee CA, Owens D, Bray G, et al: Pharmacokinetics of recombinant factor VIII (Recombinate) using one-stage clotting and chromogenic factor VIII assay. Thromb Haemost 82:1644-1647, 1999.
13. Fijnvandraat K, Berntorp E, ten Cate JW, et al: Recombinant, B-domain deleted factor VIII (r-VIII SQ): Pharmacokinetics and initial safety aspects in hemophilia A patients. Thromb Haemost 77:298-302, 1997.

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-UPDATE U (1-888-873-2838).

Baxter Healthcare Corporation

Westlake Village, CA 91362 USA

U.S. License No. 140

Printed in USA

NDC 0944-2940-01/02/03/04

Issued 2003

Appendix C: Documentation of FDA Marketing Approval

Product Approval Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

July 25, 2003

Our STN: BL 125063/0

Ms. Arlene Vidor
Baxter Healthcare Corporation
One Baxter Way
Westlake Village, California 91362

Dear Ms. Vidor:

We have approved your Biologics License Application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method under Department of Health and Human Services U.S. License No. 0140. Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method is also indicated in the perioperative management of patients with hemophilia A.

Under this license, you are approved to manufacture Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method drug substance at the Baxter Healthcare Corporation facility in Neuchâtel, Switzerland. The final formulated product will be manufactured and filled at the Baxter Healthcare Corporation facility in ----------. Final packaging/labeling will take place at the Baxter Healthcare Corporation facility in ----------. You may label your product with the proprietary name ADVATE, and will market it in 250 IU/vial, 500 IU/vial, 1000 IU/vial and 1500 IU/vial dosage forms.

The dating period for Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method shall be 18 months from the date of manufacture when stored at 2 – 8 oC. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be ---------- when stored at -------. The expiration date for the packaged product, Antihemophilic Factor

(Recombinant), Plasma/Albumin Free Method plus Sterile Water for Injection shall be dependent on the shortest expiration date of either component.

You currently are not required to submit samples of future lots of Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method, or in the manufacturing facilities.

FDA's Pediatric Rule at 21 CFR 314.55 and 21 CFR 601.27 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party intervenors have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage and specific requirements of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

We acknowledge your written commitments as described in your letters of 9 October 2002, 9 April 2003, and 15 July 2003 as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

Information regarding these may be publically disclosed on the agency's web site (http://cdsml1.cder.fda.gov/pmc/index.cfm), in the agency's annual Federal Register report on postmarketing studies and in the agency's special report to Congress.

1. To submit a protocol within six (6) months of the date of product approval for the conduct of an adequately-powered randomized study of the product in routine prophylaxis which compares 2 different dosing regimens/frequencies. To initiate the study within six (6) months of the date that FDA conveys to you its agreement with the proposed study design, and, once the study has been completed, to file the final study report of the study to both the Investigational New Drug Application (IND) and BLA under 21 CFR 601.70 in a timely manner.
2. 2. To submit a protocol within 12 months of the date of product approval for the conduct of a randomized study of the product in surgery, comparing the safety and efficacy of the product administered by intermittent bolus infusion versus continuous infusion. To initiate the study within six (6) months of the date that FDA conveys to you its agreement with the proposed study design, and, once the study has been completed, to file the final study report of the study to both the IND and BLA under 21 CFR 601.70 in a timely manner. Depending on CBER's judgment of the adequacy of the data regarding the use of Antihemophilic Factor (Recombinant), Plasma/Albumin Free Methodadministered by continuous versus intermittent bolus infusion, which is to be submitted to CBER by the end of 2003 in the form of an interim report for ongoing clinical study # 069902, CBER reserves the right to consider that the submission of such data from study # 069902 may obviate the need and phase IV requirement to conduct the randomized study described in the first part of this paragraph.
3. To complete and report to the IND and BLA in a timely fashion the results of the following ongoing and planned clinical studies:

a. Protocol # 060102 - continuation study in PTPs (target end of Q4, 2004 to beginning of 2005)
b. Protocol # 069902 - the ongoing surgery study (target end of Q4, 2004)
c. Protocol # 060101 - the ongoing pediatric PTP study (target beginning to mid 2005)
d. Protocol # 060103 - This pediatric study involving previously untreated patients is targeted to start in early 2004. Baxter will submit a report of this study to both the IND and BLA in a timely fashion after the study is completed.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

4. ----------

5. ----------

6. To submit to CBER a complete summary of all Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method lots produced during each quarter-year. This summary will include the lot numbers for all lots released, as well as a list of lots that were not released and the reason(s) for non-release.

   To submit each quarterly report electronically or as a paper submission (in triplicate) addressed as follows:

   Center for Biologics Evaluation and Research
   Attention: Office of Blood Research and Review
   HFM-99, Room 200N
   1401 Rockville Pike
   Rockville, MD 20852-1448

   To submit to CBER samples and protocols for every 5th lot of each dosage strength manufactured to the following address:

   Center for Biologics Evaluation and Research
   Attention: Sample Custodian, HFM-672
   Bldg. NLRC - B, Room 113
   5516 Nicholson Lane
   Kensington, MD 20895

7. With reference to the distribution of Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method into the US Market: As stated in your memorandum dated September 18, 2002, "It [is] the intention of Baxter to manufacture lots of rAHF-PFM Final Drug Product (FDP) for commercial distribution beginning – ---------- (including lot --------) pending approval of the Biologics License Application (BLA)." ----------

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125063. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN 125063. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

You must submit the following information in accordance with 21 CFR 601.28 and 601.70:

- a status summary of each reportable commitment in your annual report to the BLA;
- expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

You may refer to the "Draft" Guidance for Industry (April 2001): Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997.
You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports under 21 CFR 600.81. You should submit postmarketing adverse experience reports and distribution reports to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Prominently identify all adverse experience reports as described in 21 CFR 600.80.
You must submit reports of biological product deviations under 21 CFR 600.14. You promptly should identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.
Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.
All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have submitted data to support such claims to us and had them approved.

Sincerely,

--- signature ---

Basil Golding, M.D.
Acting Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Appendix D: Documentation of AWPs Determined and Published by Independent Pricing Services

PROD/MFR NDC AWP DP OBC

ACTIMMUNE (Intermune)
interferon gamma-1b
SOL, SC (VIAL)
2 million iu/0.5 ml,
0.5 ml 64116-0011-01 247.34
0.5 ml 12s 64116-0011-12 2698.20

ACTIQ (Cephalon)
fentanyl citrate
LOZ, BC (BERRY)
0.2 mg, 30s ea, C-II .. 63459-0502-30 262.00
0.4 mg,
30s ea, C-II 63459-0504-30 334.00
0.6 mg,
30s ea, C-II 63459-0506-30 409.00
0.8 mg,
30s ea, C-II 63459-0508-30 484.00
1.2 mg,
30s ea, C-II 63459-0512-30 630.00
1.6 mg,
30s ea, C-II 63459-0516-30 776.00

ACTIVASE (Genentech)
alteplase, recombinant
PDS, IV (W/DILUENT)
50 mg, ea 50242-0044-13 1487.06
100 mg, ea 50242-0085-27 2974.13

ACTONEL (P&G Pharm)
risedronate sodium
TAB, PO, 5 mg, 30s ea 00149-0471-01 75.53
30 mg, 30s ea 00149-0470-01 528.65
(DOSEPACK)
35 mg, 4s ea 00149-0472-01 70.49

ACTOS (Takeda)
pioglitazone hydrochloride
TAB, PO, 15 mg, 30s ea ... 64764-0151-04 99.65
90s ea 64764-0151-05 298.91
500s ea 64764-0151-06 1660.67
30 mg, 30s ea 64764-0301-14 159.53
90s ea 64764-0301-15 478.61
500s ea 64764-0301-16 2658.89
45 mg, 30s ea 64764-0451-24 173.05
90s ea 64764-0451-25 519.17
500s ea 64764-0451-26 2884.27

ACULAR (Allergan Inc)
ketorolac tromethamine
SOL, OP, 0.5%, 3 ml 00023-2181-03 36.80
5 ml 00023-2181-05 61.33
10 ml 00023-2181-10 122.65

ACYCLOVIR (Alpharma USPD)
SUS, PO, 200 mg/5 ml,
480 ml .... 00472-0082-16 118.55 AB
CAP, PO, 200 mg, 100s ea 00228-2605-11 111.92 AB
500s ea .... 00228-2605-50 530.71 AB
TAB, PO, 400 mg, 100s ea 00228-2606-11 216.97 AB
500s ea .... 00228-2606-50 949.30 AB
800 mg, 100s ea ...... 00228-2607-11 421.67 AB
500s ea .... 00228-2607-50 1854.25 AB

(Biovail Pharm) *See ZOVIRAX*

(Ivax Pharm)
CAP, PO, 200 mg, 100s ea 00172-4266-60 111.88 AB
500s ea .... 00172-4266-70 530.68 AB
TAB, PO, 400 mg, 100s ea 00172-4267-60 216.91 AB
500s ea .... 00172-4267-70 947.30 AB
800 mg, 100s ea ...... 00172-4268-60 421.60 AB
500s ea .... 00172-4268-70 1751.09 AB

(Mylan)
CAP, PO, 200 mg, 100s ea 00378-2200-01 111.95 AB
500s ea .... 00378-2200-05 530.46 AB
TAB, PO, 400 mg, 100s ea 00378-0253-01 217.00 AB
800 mg, 100s ea ...... 00378-0302-01 421.70 AB

(Par)
CAP, PO, 200 mg, 100s ea 49884-0565-01 111.67 AB
TAB, PO, 400 mg, 100s ea 49884-0566-01 216.72 AB
800 mg, 100s ea ...... 49884-0567-01 421.42 AB

(Teva)
CAP, PO, 200 mg, 100s ea 00093-8940-01 97.20
500s ea .... 00093-8940-05 461.70 AB
TAB, PO, 400 mg, 100s ea 00093-8943-01 188.60 AB
500s ea .... 00093-8943-05 895.85 AB
800 mg, 100s ea ...... 00093-8947-01 366.65 AB
500s ea .... 00093-8947-05 1741.59 AB

(Watson)
CAP, PO, 200 mg, 100s ea 00591-2692-01 97.70 AB
500s ea .... 00591-2692-05 464.08 AB
TAB, PO, 400 mg, 100s ea 00591-0335-01 216.72 EE
500s ea .... 00591-0335-05 1029.42 EE
800 mg, 100s ea ...... 00591-0336-01 421.42 EE
500s ea .... 00591-0336-05 2001.75 EE

ADALAT CC (Bayer Corp.)
nifedipine
TER, PO, 30 mg, 100s ea 00026-8841-51 155.05 AB1
1000s ea 00026-8841-54 1550.50 AB1
60 mg, 100s ea 00026-8851-51 276.20 AB1
1000s ea 00026-8851-54 2761.98 AB1
90 mg, 100s ea ...... 00026-8861-51 323.71 BC

ADALIMUMAB/ISOPROPYL ALCOHOL
(Abbott Labs) *See HUMIRA*

ADAPALENE
(Galderma) *See DIFFERIN*

ADDERALL (Shire US Inc.)
amphetamine salt combination
TAB, PO, 5 mg,
100s ea, C-II ...... 54092-0371-01 181.74 AB
7.5 mg,
100s ea, C-II ...... 54092-0372-01 181.74 AB
10 mg,
100s ea, C-II ...... 54092-0373-01 181.74 AB
12.5 mg,
100s ea, C-II ...... 54092-0374-01 181.74 AB
15 mg,
100s ea, C-II ...... 54092-0375-01 181.74 AB
20 mg,
100s ea, C-II ...... 54092-0376-01 181.74 AB
30 mg,
100s ea, C-II ...... 54092-0377-01 181.74 AB

ADDERALL XR (Shire US Inc.)
amphetamine salt combination
CER, PO, 10 mg,
100s ea, C-II 54092-0383-01 298.61
20 mg,
100s ea, C-II 54092-0387-01 298.61
30 mg,
100s ea, C-II 54092-0391-01 298.61

ADIPEX-P (Gate)
phentermine hydrochloride
CAP, PO, 37.5 mg,
100s ea, C-IV ...... 57844-0019-01 181.75 AA
TAB, PO, 37.5 mg,
100s ea, C-IV ...... 57844-0009-01 178.55 AA
1000s ea, C-IV ..... 57844-0009-10 1363.94 AA

ADOXA (Bioglan)
doxycycline
TAB, PO, 50 mg, 100s ea .. 62436-0728-01 208.04
(PROTECT FROM LIGHT)
75 mg, 100s ea 62436-0730-01 258.30
500s ea 62436-0730-05 1096.20
100 mg, 50s ea 62436-0729-03 169.84
250s ea 62436-0729-04 816.13

ADRIAMYCIN (Bedford)
doxorubicin hydrochloride
SOL, IV (S.D.V.)
2 mg/ml, 5 ml 10s .... 55390-0235-10 132.00 AP
(S.D.V.,PF)
2 mg/ml, 10 ml 10s ... 55390-0236-10 264.00 AP
(S.D.V.)
2 mg/ml, 25 ml .... 55390-0237-01 64.80 AP
(M.D.V.)
2 mg/ml, 100 ml ..... 55390-0238-01 264.00 AP
PDS, IV (S.D.V.,PF)
10 mg, 10s ea .... 55390-0231-10 132.00 AP
20 mg, 10s ea .... 55390-0232-10 264.00 AP

ADRUCIL (Pharmacia Corp)
fluorouracil
SOL, IV (VIAL)
50 mg/ml, 10 ml ..... 00013-1036-91 3.07 2.56 AP
50 ml .... 00013-1046-94 15.39 12.83 AP
100 ml .... 00013-1056-94 30.78 25.65 AP

ADRUCIL (Sicor Pharm., Inc.)
fluorouracil
SOL, IV (S.D.V.)
50 mg/ml, 10 ml 10s . 00703-3015-13 37.50 AP
(PHARMACY BULK PACKAGE)
50 mg/ml, 50 ml 5s ... 00703-3018-12 80.31 AP
100 ml 5s .... 00703-3019-12 160.63 AP

ADVAIR DISKUS 100/50 (GSK Pharm)
fluticasone propionate/salmeterol xinafoate
DSK, IH, 28s ea 00173-0695-02 79.67
60s ea 00173-0695-00 118.04

ADVAIR DISKUS 250/50 (GSK Pharm)
fluticasone propionate/salmeterol xinafoate
DSK, IH, 28s ea 00173-0696-02 98.32
60s ea 00173-0696-00 149.41

ADVAIR DISKUS 500/50 (GSK Pharm)
fluticasone propionate/salmeterol xinafoate
DSK, IH, 28s ea 00173-0697-02 138.28
60s ea 00173-0697-00 205.37

ADVATE (Baxter)
KIT, MR (APPROX. 1000 IU/VIAL,PF)
1 iu, ea 00944-2940-03 1.66
(APPROX. 1500 IU/VIAL,PF)
1 iu, ea 00944-2940-04 1.66
(APPROX. 250 IU/VIAL,PF)
1 iu, ea 00944-2940-01 1.66
(APPROX. 500 IU/VIAL,PF)
1 iu, ea 00944-2940-02 1.66

ADVICOR (Kos Pharm)
lovastatin/niacin
TER, PO (CAPLET)
20 mg-500 mg, 90s ea 60598-0006-90 164.32
20 mg-750 mg,
90s ea 60598-0007-90 200.58
20 mg-1000 mg,
90s ea 60598-0008-90 214.18

AEROBID (Forest Pharm)
flunisolide
ARO, IH, 0.25 mg/actuation,
7 gm 00456-0672-99 73.87

AEROBID-M (Forest Pharm)
flunisolide
ARO, IH (MENTHOL)
0.25 mg/actuation,
7 gm 00456-0670-99 73.87

AEROCHAMBER (Forest Pharm)
spacer, inhalation
DEV, NA, ea 00456-3154-67 33.88
(W/MASK)
ea 00456-0745-13 45.67
(W/MASK, LARGE)
ea 00456-0746-13 45.67
(W/MASK,SMALL)
ea 00456-0744-13 45.67

AEROHIST (Aero Pharm)
chlorpheniramine maleate/methscopolamine nitrate
TER, PO (CAPLET)
8 mg-2.5 mg, 100s ea 66440-0082-51 135.99

AGALSIDASE BETA
(Genzyme) *See FABRAZYME*

AGGRENOX (Boehr Ingelheim Phar)
aspirin/dipyridamole
CER, PO, 25 mg-200 mg,
60s ea 00597-0001-60 128.60

AGRYLIN (Shire US Inc.)
anagrelide hydrochloride
CAP, PO, 0.5 mg, 100s ea .. 54092-0063-01 651.47
1 mg, 100s ea 54092-0064-01 1302.92

AHF VIII (RECOMBINANT) SUCROSE FORMULATED
(Aventis Behring) *See HELIXATE FS*

(Bayer Corp.) *See KOGENATE FS*

AHF VIII:C HUMAN/VON WILLEBRAND FACTOR
(Aventis Behring) *See HUMATE-P*

ALBUMARC (Amer Red Cross-Plasm)
albumin human
SOL, IV, 5%, 250 ml 52769-0450-25 98.50
500 ml 52769-0450-50 197.00
25%, 50 ml 52769-0451-05 98.50
100 ml 52769-0451-10 197.00

ALBUMIN HUMAN

(Alpha Therapeutic) *See ALBUTEIN*

(Alpine Biologics) *See ALBUMIN-ALPINE*

(Amer Red Cross-Blood)
SOL, IV (PF)
5%, 250 ml 64193-0250-25 98.50
500 ml 52769-0250-50 197.00

(Amer Red Cross-Plasm)
SOL, IV, 25%, 50 ml 52769-0251-05 98.50
100 ml 52769-0251-10 197.00

(Amer Red Cross-Plasm) *See ALBUMARC*

(Aventis Behring) *See ALBUMINAR-25*

(Aventis Behring) *See ALBUMINAR-5*

(Baxter Bio) *See BUMINATE*

(Bayer Corp.) *See PLASBUMIN-25*

(Bayer Corp.) *See PLASBUMIN-5*

(ZLB Bioplasma) *See ALBURX*

ALBUMIN-ALPINE (Alpine Biologics)
albumin human
SOL, IV (W/ADMIN. SET/SAFETY NDL)
5%, 250 ml 63546-0310-25 99.00
500 ml 63546-0310-50 198.00
25%, 50 ml 63546-0251-05 99.00
100 ml 63546-0251-10 198.00

ALBUMINAR-25 (Aventis Behring)
albumin human
SOL, IV, 25%, 20 ml 00053-7680-01 40.00
50 ml 00053-7680-32 112.50
(W/OUT IV SETS)
25%, 100 ml 00053-7680-33 225.00

ALBUMINAR-5 (Aventis Behring)
albumin human
SOL, IV, 5%, 50 ml 00053-7670-06 40.00
250 ml 00053-7670-31 112.50
500 ml 00053-7670-32 225.00
(W/ADMIN. SET)
5%, 1000 ml 00053-7670-03 360.00

ALBURX (ZLB Bioplasma)
albumin human
SOL, IV, 5%, 250 ml 44206-0310-25 58.00
500 ml 44206-0310-50 116.00
25%, 50 ml 44206-0251-05 58.00
100 ml 44206-0251-10 116.00

ALBUTEIN (Alpha Therapeutic)
albumin human
SOL, IV, 5%, 250 ml 49669-5211-01 90.00
500 ml 49669-5211-02 180.00
25%, 20 ml 49669-5213-01 36.00
50 ml 49669-5213-02 90.00
100 ml 49669-5213-03 180.00

ALBUTEROL (Andrx Pharmaceutical)
ARO, IH, 0.09 mg/actuation,
17 gm .... 62037-0794-44 28.70 AB

(Ivax Pharm)
ARO, IH, 0.09 mg/actuation,
17 gm .... 00172-4390-18 29.79 AB

(Schering) *See PROVENTIL*

(Warrick)
ARO, IH, 0.09 mg/actuation,
17 gm .... 59930-1560-01 21.41 BN
(REFILL)
0.09 mg/actuation,
17 gm .... 59930-1560-02 19.79 BN

ALBUTEROL SULFATE (Alpharma USPD)
SOL, IH (PF)
0.083%, 3 ml 30s ...... 00472-0831-30 37.08 AN
3 ml 60s .... 00472-0831-60 74.16 AN
SYR, PO (BERRY)
2 mg/5 ml, 480 ml ... 00472-0825-16 40.15 AA

(GSK Pharm) *See VENTOLIN HFA*

(Hi-Tech)
SOL, IH, 0.083%, 3 ml 25s 50383-0742-25 30.35 AN
SYR, PO, 2 mg/5 ml, 473 ml 50383-0740-16 39.60 AA
SOL, IH, 0.5%, 20 ml ..... 50383-0741-20 16.50 AN

NATIONAL DRUG DATA FILE PRODUCT UPDATE REPORT
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00944-2940-01	ADVATE 250IU KIT SDV,PLASMA-ALBM FREE	1.000 EA	$1.50	$0.00	$1.88	03/07/28
RX OBC: SB					DATE OF CHANGE: ___/___/___	
00944-2940-02	ADVATE 500IU KIT SDV,PLASMA-ALBM FREE	1.000 EA	$1.50	$0.00	$1.88	03/07/28
RX OBC: SB					DATE OF CHANGE: ___/___/___	
00944-2940-03	ADVATE 1000IU KIT SDV,PLASMA-ALBM FREE	1.000 EA	$1.50	$0.00	$1.88	03/07/28
RX OBC: SB					DATE OF CHANGE: ___/___/___	
00944-2940-04	ADVATE 1500IU KIT SDV,PLASMA-ALBM FREE	1.000 EA	$1.50	$0.00	$1.88	03/07/28
RX OBC: SB					DATE OF CHANGE: ___/___/___	